EXHIBIT 10

Advisory Committee Briefing Document
February 7, 2000

Medical Officer's Gastroenterology Advisory Committee Briefing Document
Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products: HFD-550

NDA 20,998: Supplement # 9
Sponsor: Searle

Name of drug: Celecoxib (Celebrex ™)

Dose 400mg bid

Subject of Consult: Review of Celecoxib Long-Term Arthritis Safety Study (CLASS)

Materials reviewed: Protocols and Study reports for N49-98-02-102 and N49-98-02-035

Submission date: June 12, 2000

Reviewer: Lawrence Goldkind M.D.

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Background

Celebrex (C) was approved in 1998 for the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA). The approved dose was 200 to 400 mg daily. In 1999 C was approved for the treatment of Familial Adenomatous Polyposis (FAP) at a dose of 800 mg daily. This product is a highly selective inhibitor of cyclooxygenase-2 (COX-2). The drive to develop highly selective cyclooxygenase (COX) inhibitors was based on the hopes that the safety profile would be improved compared to less selective agents. Upper gastrointestinal ulcers complicated by pain, bleeding and perforation are a labeled complication of NSAIDs. Of the two isoforms, COX-1, a constituitively-generated enzyme has been considered critical to the maintenance of the upper gastrointestinal mucosal integrity. Physiological mechanisms that are linked to "maintenance" effects of COX-1 generated prostaglandins include gastric mucous production, bicarbonate secretion and mucosal blood flow. Inhibition of this enzyme has been linked to the gastrointestinal toxicity of NSAIDs. COX-2 is upregulated in inflammatory conditions. Since the identification of the second isoform of COX, it has been hoped that selective inhibition of this isoform would effectively treat inflammatory conditions and pain with less gastrointestinal toxicity. The original NDA included extensive safety data related to upper gastrointestinal ulceration that are reflected in the product label. C was associated with fewer endoscopically defined (as opposed to symptomatically defined) ulcers compared to ibuprofen and naproxen. The studies submitted to the Division did not however, replicate a difference between C and diclofenac at this specified endpoint. Furthermore, the studies reviewed to date have not differentiated C from other NSAIDs studied in terms of gastrointestinal symptoms and clinically meaningful ulcers. Some GI symptoms appear to be more commonly associated with C compared to the other NSAIDs studied while some were more common in specific comparators.

Comparative safety claims are susceptible to bias by selectively defining the events of interest without incorporating other potentially important toxicities. Comparative study of symptoms and clinically relevant outcomes must be linked to dose and specific comparator. Comparative study of safety and subsequent safety claims are intrinsically different than the well ploughed area of drug efficacy. Efficacy is typically established for a particular beneficial effect. Study can therefore be based on prespecified definitions, objectives, instruments of measurement and statistical analysis. Safety, by comparison is multifaceted and therefore less easily studied and quantified. Specific safety claims other than those associated with ultimate endpoints such as death or permanent disability are difficult to study in an unbiased way that includes the concept of overall safety.

Upper gastrointestinal toxicity has been identified as a major health risk associated with the use of NSAIDs. Some estimates of the number of deaths due to the complications of gastrointestinal bleeding and perforation attributed to these products as a class are in the range of 10-20,000 per year in the United States. Based on these estimates, NSAIDs contain a generic warning of GI risk. Thus, gastrointestinal toxicity appears to be an appropriate specific safety issue for study. COX-2 selective inhibitors hold the promise of having less GI toxicity than less selective agents. Just as relative specificity of COX

isoenzyme inhibition exists, so does the possibility of **relative** specificity of GI safety. Available information about the toxicity of NSAIDs suggests that each NSAID most likely has a somewhat unique profile. The study of relative safety has been limited by the difficulties inherent in safety studies compounded by the difficulties in comparative studies of many agents, at different doses, over long periods of time, using different endpoints in heterogeneous populations. The presence of generic products further discourages large expensive comparative studies.

The most daunting challenge in the study of GI safety is that the most important outcomes of bleeding, obstruction and perforation are rare events, estimated to occur in less than several percent of patients on chronic NSAIDs per year. (The estimates of perforations, ulcers and bleeding that appear in the GI warning section of NSAID labels include ulcers associated with pain alone, without the more serious complications). Therefore, large studies are required.

Once the morbid outcomes of bleeding, obstruction and perforation are excluded, it becomes difficult to define an appropriate safety comparison for NSAIDs. The majority of ulcers are painless and up to 30% of patients on NSAIDs experience abdominal pain. The correlation between UGI symptoms and mucosal damage produced by NSAIDs is poor. Gastric adaptation to the effects of NSAIDs has been well described and UGI lesions are frequently transient. This produces new difficult questions. Is abdominal pain less or more significant than other GI symptoms such as diarrhea, nausea or vomiting? Are such symptoms more relevant than other toxicities such as renal or hepatic damage?

The original NDA database suggested that C did **not** differentiate from the three comparators studied (ibuprofen, diclofenac and naproxen) in terms of symptoms nearly as it did for endoscopic ulcers. Based on these findings, the current product label includes the same warnings regarding gastrointestinal toxicity that less selective NSAIDs have. Based on the theoretical advantages of COX selectivity discussed previously and the endoscopic data that appears in the product label, C has been widely accepted as "safer" than previously approved NSAIDs [1]. Although it is tempting to accept the development of asymptomatic ulcers as a meaningful endpoint and a surrogate for clinically relevant outcomes, there is inadequate evidence to date to accept this as fact. The clinical outcome trial entitled, "MUCOSA" published in 1995 in conjunction with other studies of endoscopically defined ulcers associated with the use of NSAIDs and misoprostol are suggestive of a correlation. This study did not have prespecified outcomes and a statistical plan that allowed for firm conclusions. Furthermore, this study cannot be extrapolated to all other potentially "gastroprotective" drugs. Therefore, adequate evidence of a uniquely improved GI safety profile for C was not established in the original NDA.

The Medical Officer's Consult Review from the Division of Gastrointestinal and Coagulation Drug Products dated December 1998 reflects the view at the time of the original NDA submission that endoscopic ulcers had not been validated as surrogates for clinically meaningful events. The submitted comparative information on endoscopic ulcers was not accepted by the Division at the time of the original NDA submission as

adequate to change the NSAID GI warning template on the Celebrex label. The final recommendation of the Consult review dated December 1998 stated that:

" It is recommended that future studies with well defined and clinically important UGI endpoints be planned to address safety claims related to clinically significant UGI endpoints. These studies and postmarketing experience will be needed to accurately define the relationship between this new molecular entity and the class of drugs currently in use and described as NSAIDs."

Databases are inadequate at the time of marketing to fully define the safety profile of a new drug. This is particularly true of new molecular entities and drug classes. (Some authors contend that COX-2 selective agents represent a new class. The World Health Organization has placed such agents in a separate class than traditional NSAIDs that are less selective.) The wide acceptance evidenced by many millions of prescriptions in the first year of marketing reflects acceptance of C as a safer alternative to traditional NSAIDs. However, clinically relevant safety endpoints are rare and may be missed in a database of even several thousand subjects. Authors outside the FDA have voiced concern over this as well. The following extensive quote is taken from a lead editorial in the journal *Rheumatology*, September 2000.

> " While it is still true that Cox-1 is expressed constitutionally in most cells and Cox-2 is induced in sites of inflammation and other pathology, recent careful work has clarified several physiological situations in which Cox-2 inhibitors in the clinic are understood only partly at present...
>
> The driving force behind the rapid and forceful cooperation between basic science and drug development was concern about the serious toxicities of conventional NSAIDs and aspirin, not least the increased fatalities resulting from gastrointestinal bleeding and ulcer perforation. Those who are skeptical about extrapolation form databases such as ARAMIS are referred to a Finnish study that identified 30 fatalities from the use of NSAIDs in that country in a single year. Cox-2 is up-regulated in the inflamed joint, and the hypothesis was that selective inhibition of the inducible Cox-2 isoenzyme would offer therapeutic efficacy without this severe toxicity. Endoscopic data from clinical trials support this hypothesis, *but information about the risk of serious events, i.e. bleeding and perforation is still not at hand. New insights into the biologic function of Cox-2 should caution us from the uncritical use of Cox-2 inhibitors. There is a convincing evidence from published trials that celecoxib is equivalent but not superior to conventional NSAIDs in the symptomatic control of osteoarthritis and rheumatoid arthritis. However, long-term safety data can be established only with time and, as with all new types of drugs, we should be vigilant in recognizing possible new types of problems. The questions that must still be addressed concern the ultimate consequences of selective inhibition of Cox-2 and its biological functions"* 1
>
> (italics, reviewer's addition)

Another author in a review article in the New England Journal of Medicine stated that:

" In spite of enthusiasm for these promising new agents NSAIDs, some questions remain regarding their highly selective inhibition of cyclo-oxygenase-2. For example, cyclo-oxygenase-2 might generate endogenous prostanoids that are biologically important....

..although the highly selective cyclo-oxygenase-2 inhibitors offer considerable promise in the treatment of inflammatory arthritidies, careful surveillance will be important to determine their ultimate benefit and safety profile." [2]

The Division and the sponsor have agreed that indirect validation of the surrogacy of endoscopic ulcers for clinically meaningful upper gastrointestinal injury as well as a desire for a larger controlled database for overall safety assessment warranted a large controlled study of clinically relevant safety outcomes. While upper gastrointestinal tract injury was the primary and prespecified endpoint, the sponsor and the Division shared the concerns noted by the author of reference #1.

The primary medical officer's review will assess the overall safety profile generated by the current submission. This GI consult review will deal primarily with the gastrointestinal outcomes from studies 102 and 035.

Clinical studies

N49-00-035/ N49-00-102

The final protocol and a summary of amendments appear in Appendix I. Reviewer comments related to study design are described below. These studies were identical except for the comparator NSAID employed. The prespecified intent was to compare the combined C groups from the two studies and compare them to the composite of both NSAIDs and subsequently to each individual NSAID.

Objectives: In the completed study report the stated primary objective was to compare the incidence of clinically significant UGI events (CSUGIEs) associated with celecoxib 400 mg bid to that associated with ibuprofen 800 mg tid and diclofenac 75 mg bid.

Reviewer's comments related to objectives

A. Dose selection:

The choice of dose for celecoxib is twice the labeled dose for rheumatoid arthritis. The dose of diclofenac and ibuprofen are within the commonly used range of each for the treatment of OA and RA. While the NSAID comparators have been in use for years and have well-established dose ranges in practice, celecoxib is a new molecular entity and has a less well established efficacy and dose ranging profile. A successful safety comparison may suggest to consumers that there is room to "push" the dose of a drug with proposed analgesic as well as anti-inflammatory properties. This phenomenon of "dose creep" is particularly relevant in the treatment of pain when currently available therapies leave most patients with some residual pain (absence of total pain relief). The widely held expectation that new COX-2 selective agents will have little to no potential for UGI toxicity requires a robust proof of principle. Comparative safety information therefore will be most meaningful for a high dose of celecoxib.

The recent recommendation by the advisory committee for the Division of Oncologic Drug Products for accelerated approval of celecoxib at a dose of 800 mg per day for the treatment of FAP was based on a risk/benefit assessment under the assumption that this high dose of celecoxib would not be associated with a meaningfully higher adverse event profile than the more extensively tested anti-inflammatory doses. Future potential indications (particularly in the area of **_disease prevention_** where the extent and duration of exposure will be greatly expanded) for selective Cox-2 inhibitors will need to be assessed based on a robust safety database. The safety study of the 800-mg daily dose of C (celecoxib) represents a safety study .

The UGI toxicity of NSAIDs is generally believed to be dose related. In the endoscopic studies of celecoxib presented in the original NDA, there was no consistent or convincing evidence of a dose related increase in ulcer rates across the several studies. The studies however were not designed to test this hypothesis.

B. Selection of comparators:

The original protocol included three NSAIDs (naproxen, ibuprofen and diclofenac). A study result demonstrating a lower rate of CSUGIEs in the celecoxib group compared to three widely prescribed NSAIDs would have been robust evidence of a UGI safety advantage compared to previously approved NSAIDs. The original protocol was amended to include only two comparators. This limits the potential generalizability of results.

C. Primary objective:

The primary objective in the __final__ form of the study report reproduced above suggests that the comparison to NSAIDs __as a group__ was the primary goal. However, this was not the case.

"The primary comparison will be the incidence of clinically significant UGI adverse events associated with SC-58635 400 mg BID to that associates with ibuprofen 800 mg TID and __separately__ to that associated with diclofenac 75 mg BID... The null hypothesis being tested is that there is no difference in the incidence of clinically significant UGI adverse events between the SC-58635 and __each__ of the NSAID groups (ibuprofen and diclofenac)." (protocol dated October 26, 1998: bolding and underling by reviewer)

The sample size calculation was based on the pairwise comparison of pooled celecoxib and __each__ of the NSAIDs. The clinical importance of statistically significant superiority to each of the comparators was reflected in the statistical plans in the __original protocol__.

The Division has considered generalizability to be statistically based. Thus comparisons to each of the NSAID comparators were defined in the original protocol. In order to avoid the statistical pitfall of multiple comparisons, a stepwise approach was prespecified. The protocol stated that the celecoxib groups from the two studies would be pooled for comparison to the pooled NSAID groups first. __Only if there was a statistically significant difference between the pooled celecoxib groups compared to the pooled ibuprofen and diclofenac groups would further comparisons to each NSAID be performed to assess the generalizability of the safety comparison.__

Demonstration of the consistency of superiority of celecoxib across NSAID comparators would be critical to the generalizability of study results. Superiority to only a single NSAID comparator would not support a proof of principle regarding the UGI safety benefits of a Cox-2 inhibitor. The low overall incidence of CSUGIEs may make comparator-specific statistical significant differences difficult to demonstrate. Similarity in trend however, would be critically important.

D. Definition of endpoint:

The definition of CSUGIEs chosen by the sponsor is reproduced in Appendix I. This is a clinically meaningful definition and represents a major advance in the study of UGI toxicity of NSAIDs. Many previous studies of NSAID toxicity including the often-cited MUCOSA [2] trial have failed to rigorously prespecify endpoint events. The sponsor has made a methodological commitment in the current trial to a rigorous study of truly significant UGI adverse events. __Endoscopically defined ulcers__ do not independently represent a clinically important event. While symptomatic ulcers are important; the lack of adequate correlation between UGI symptoms and ulcers in subjects on NSAIDs creates a significant artifact when using symptomatic ulcers as __the__ primary endpoint of an outcome study. The sponsor states in the current submission:

"In addition to the pathologic effects on the GI tract mucosa, NSAIDs also produce GI intolerance, which manifests as nonspecific symptoms such as dyspepsia, abdominal pain, and nausea. Because they often occur in the absence of ulcers or ulcer complications, these symptoms are poor positive predictors of serious GI toxicity."

Section 1.2 of Integrated summary of safety, benefit and risks

A recently published review appearing in the New England Journal of Medicine states:

" At least 10-20% of patients have dyspeptic symptoms during NSAID therapy. However, such symptoms are poorly correlated with the endoscopic appearance and severity of mucosal injury, since up to 40% of persons with endoscopic evidence of erosive gastritis are asymptotic, and conversely, as many as 50% of patients with dyspepsia have normal-appearing mucosa." [2]

The establishment of a CSUGIE (as defined in Appendix I) as the primary endpoint with the addition of symptomatic ulcers only as a secondary endpoint is a major strength of the current study The low event rate for CSUGIEs requires a large study population for adequate power.

An "alternative" definition was also developed to define a more serious event (see appendix I). This alternative definition required criteria that defined a more serious endpoint by requiring documentation of major blood loss based on hypotension and fall in hemoglobin.

OA and RA are felt by some to represent different risk groups for CSUGIEs. There are emerging data to suggest that these conditions may be associated with different risk profiles for a multitude of co-morbid conditions. The inclusion of both populations in the study may therefore allow generalizability of the GI as well as overall safety profiles of the three comparators.

In summary:

- *Choice of celecoxib dose*

- *Duration of study*

- *Multiplicity of comparators*

- *Choice of primary endpoint and definition of such as outlined in Appendix I*

- *Inclusion of both RA and OA patients*

- *Size*

all establish this study as an important and rigorous evaluation of the UGI safety profile of celecoxib.

Based on the size and rigor of the protocol in ascertaining safety information in a controlled setting, this study may also provide valuable information regarding the relative overall safety of celecoxib and the comparator NSAIDs. Other prespecified safety endpoints for analysis included:

1. *Laboratory parameters are noted in appendix I. These included potentially important renal function and hematological parameters.*

2. *Symptomatic ulcers without evidence of perforation bleeding or obstruction*

Reviewer's comments related to study design:

The study was well designed with adequate detail provided for randomization, double-blinding, and appropriately timed follow-up. An optimal study of chronic drug safety involves long term follow-up. The treatment period for this study was defined as up to 52 weeks in protocol 102 and 65 weeks in protocol 035. In order to maximize the chronic safety data obtainable from this study, a minimum of 6 months exposure for all enrolled subjects was included in the protocol, even if the statistically prespecified number of CSUGIEs was reached sooner. The sponsor enhanced the value of this safety study by incorporating this minimum exposure in the protocol.

The absence of a screening endoscopy in a study population recently on NSAIDs may allow for the inclusion and therefore incorrect attribution of some ulcers, particularly early in the study. This design however is appropriate for an optimal risk assessment generalizable to clinical settings.

Inclusion criteria:

The inclusion criteria were broad, including both OA and RA suffers, both genders and all adult age groups. This is appropriate for a large safety outcome study to be generalized to a large population. Stratification based on type of arthritis may allow disease specific analysis of risk.

Exclusion criteria:

The exclusion criteria were limited, again adding generalizability to the results. Ethical considerations required the exclusion of subjects with recent active ulcer disease.
High- risk populations were otherwise not excluded.
A critically important point is the inclusion of subjects on prophylactic low-dose aspirin. This element of the study design may be expected to confound the results of the study by attributing to the Celecoxib group events that may physiologically be attributable to the Cox-1 inhibition provided by aspirin. Subanalysis in a large outcome study may allow

adequate assessment of this potential effect. The benefit of including aspirin- using subjects is critical. Currently 10-20% of Americans use aspirin prophylactically. OA and RA sufferers are enriched populations for aspirin use due to age and age-associated rates of cardiovascular disease. The sponsor has accepted the potential negative impact on the power of the study to detect a difference in event rates between the groups by including aspirin users. The generalizability of results and the safety information related to drug-drug interactions will be very important to a large portion of the population of individuals that uses NSAIDs. Since a history of cardiovascular disease has been considered by many to be an important risk factor for CSUGIEs in general, it is very important that this population be addressed.

Removal of patients from therapy or assessment:

Section 6.2.3 of the protocol describes the reasons for withdrawal. They are all reasonable. Withdrawal due to treatment failure may introduce bias based on informed censoring. This is an unavoidable issue, however.
Withdrawal due to adverse sign or symptom is likewise an unavoidable event that may introduce bias. This may be particularly true if subjects with UGI symptoms are at higher risk of developing a CSUGIE and withdraw prematurely. Withdrawal of subjects with ulcers may likewise introduce informed censoring. This is particularly true if one comparator has a higher incidence of UGI symptoms that result in a higher rate of clinically mandated evaluation of symptoms that result in the identification of UGI ulcers that do not meet the definition of a CSUGIE. Bias due to a differential withdrawal due to UGI symptoms would be minimized in the study by including a secondary endpoint of symptomatic ulcers and mandating that all subjects with both severe and less severe GI symptoms (see CSR vol.11 p53) would be evaluated for the etiology of their symptoms.

In consultation with the Division, an amendment to the protocols was made that __excluded__ from the "primary analysis", events that occurred within 48 hours after midnight following the first dose of study drug and any event occurring more than 48 hours after midnight after the last dose (unless it occurred within 2 weeks after the last dose of study medication **and** the GEC determined that it was treatment-related. This amendment was generated before the completion of the study and unblinding. It minimized the effect of confounding medications that may be taken during the window periods just before and after the study.

Treatment period

Section 6.4.1.2 of the protocol describes the ascertainment methodology for CSUGIEs as well as symptomatic ulcers. The rigor of ascertainment was adequate and well standardized for CSUGIEs. In addition to monitoring for clinically severe symptoms or signs of perforation, obstruction and bleed, an open ended question was part of each follow-up visit: "Since your last visit, have you experienced or do you currently have any symptoms that are not associated with your arthritis?"

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An element of the overall secondary objective: "Compare the overall safety and tolerability of celecoxib versus ibuprofen and diclofenac;" logically includes other GI adverse events. No formal hypotheses regarding the overall secondary objective or specifically GI adverse events were proposed. A rigorous analysis of such events would be of value. Section 6.4.3.3 notes that; "Upper GI ulcers documented by endoscopy or UGI barium x-ray with no evidence of perforation, bleeding or obstruction were categorized separately" (from CSUGIEs). The systematic approach to monitoring subjects for symptoms and signs of UGI events provided a reasonable and standardized approach to the assessment of symptomatic ulcers. The aggressive approach to monitoring may, however, result in an inflated rate compared to what would be expected in a clinical setting. While the endpoint of symptomatic ulcers may be supportive of the primary endpoint CSUGIEs, this reviewer would be cautious of overinterpretation of this endpoint independently. A post-hoc statistical analysis of the symptomatic ulcer endpoint should be predicated on statistical success at the primary endpoint or establishment of a statistical adjustment to minimize the effects of multiplicity.

Statistical methods:

The reader is also referred to the statistician's review.
The original hypothesis is discussed on pages 3-5. The statistical analysis in the final study report differs from the original protocol. The analyses in the final report are described in the excerpt below from the completed study report.

8. UGI SAFETY EVALUATION

For the two end points of primary interest within this section, namely (1) CSUGIEs (traditional definition) and (2) CSUGIEs combined with gastroduodenal ulcers (CSUGIEs/GDUs), the analyses are presented as follows:

- First Six Months of Treatment
    a. All Patients
    b. Patients not Taking Aspirin
    c. Patients Taking Aspirin
- Entire Study Period
    a. All Patients
    b. Patients not Taking Aspirin
    c. Patients Taking Aspirin

The rationale for separately considering the first six months and the entire study period is as follows. Six months of exposure represents a clinically meaningful exposure for a comparison of GI safety end points and can readily be compared to available data from the only prospective, controlled trial published on GI safety end points in patients receiving NSAIDs. (2) Additionally, disproportionate withdrawal of patients with NSAID-associated risk factors was observed over the first six months of the study, and may have artificially decreased the observed rate of clinically significant events in the NSAID groups after six months (i.e., depletion of susceptible patients). The issue of unbalanced withdrawal of patients with NSAID-associated risk factors is discussed further under "Adjustment for Informative Censoring and Risk Factor Analysis" (see Section 8. 6. below).

In addition, the subgroup analyses of patients not taking aspirin and those taking aspirin were performed because of the known confounding effect of aspirin (aspirin use at ≤325 mg/day was allowed during the study). This effect is established by studies in the literature (10,11), as well as by analyses of risk factors from the present study (Section 8. 6.), which establish low-dose aspirin as an independent cause of CSUGIEs and ulcers among patients receiving celecoxib.

Finally, the reason for presenting combined analyses of CSUGIEs/GDUs is that withdrawal of patients with ulcers that did not meet the prespecified definitions of a CSUGIE removed patients at risk (i.e., an additional source of depletion of susceptible patients). Combining the ulcer and CSUGIE data adjusts for this source of bias. Further confounding due to informative withdrawals resulting from GI adverse events may also have occurred, particularly in the diclofenac group. Differential rates of withdrawal due to GI intolerance are discussed under "Gastrointestinal Effects" (Section 10. 6. 1.). Statistical considerations relating to informative withdrawal due to GI adverse events and how this may have altered the observed rates of CSUGIEs and gastroduodenal ulcers are discussed under "Adjustment for Informative Censoring and Risk Factor Analysis" in Section 8. 6. .

The analyses of gastroduodenal, gastric, and duodenal ulcers; all reported potential CSUGIEs; all adjudicated potential CSUGIEs; and CSUGIEs analyzed according to the alternate definition were performed similarly to the traditional CSUGIE and CSUGIE/GDU analyses. However, in some cases the six-month analyses and/or the aspirin subgroup analyses are included in appendices and not addressed in the discussion of the results.

CSR p 62-63

Reviewer's comments on final statistical analysis

Given the extensive changes made post hoc to the statistical analysis a discussion follows of this reviewer's assessment of the sponsor's justifications for abandoning the original primary and secondary analyses.

A. Rational for 6-month analysis
B. Rational for imputation of event rates
C. Combined analysis of CSUGIEs and GDUs
D. Analysis based on absence of aspirin use

A. Rationale for 6-month analysis:

The rationale for analyzing the first 6 months as a meaningful endpoint independent of success at the study completion is not convincing.

i. _A 6-month study period does not reflect the anticipated clinical exposure to drug therapy or the natural history of any of the chronic diseases for which the drug is intended (Osteoarthritis, Rheumatoid Arthritis and Familial Adenomatous Polyposis/FAP). Of note is that at the FDA advisory committee meeting that considered the approval of C for use in FAP the safety profile of C was discussed in the context of required long term exposure and assumed to be superior to other NSAIDs. The surrogate endpoint of fewer polyps was accepted as a basis of accelerated approval of C for FAP with a chronic safety profile assumed to be adequately reflected in the original NDA database. Failure to differentiate from other NSAIDs over longer periods of time is of more importance than similarity over shorter periods if the results are to be truly reflective of risk._

ii. _The sponsor's rationale for limiting the study period is that the results at the end of the study do not in fact reflect the true risks due to informative censoring that occurred due to an imbalance in the withdrawal rate of the different drugs (related to adverse events). Several points are offered in response._

   a. _In a naturalistic setting of clinical use such "censoring" will take place and is in fact the setting of most relevance. If one product produces symptoms that result in a higher withdrawal rate that "spares" the occurrence of a CSUGIE, this may result in a study result that does not reflect the "biologic potential" for producing a CSUGIE. It does however reflect what can be anticipated in clinical practice with patients. One may in fact consider self- selected withdrawal from a drug due to a minor adverse event (before experiencing a more severe adverse event such as a CSUGIE) to represent a benefit of the drug's overall adverse event profile compared to a drug that is "silent" in terms of symptoms until a serious adverse event occurs. A literature on this subject exists.[11] Risk of physiologic exposure may in fact be more clinically relevant than exposure in a natural setting (that may be shortened due to intolerance). This discussion is hypothetical but indicates that there are multiple clinically relevant interpretations of a differential withdrawal rate._

b. *A review of the results (see results section) reveals that the pattern of event rate seen for diclofenac (few late events attributed by the sponsor to the loss of at-risk subjects due to early withdrawal) is also seen in the ibuprofen group despite the similarity in drop out data between C and ibuprofen. The drop out experience identified for the diclofenac group does not explain the nearly identical pattern of events seen in the ibuprofen group.*

c. *Demographic imbalances that potentially <u>favored</u> the diclofenac group were seen in the demographic results. <u>If</u> one were to post-hoc change the statistical analysis, numerous findings in addition to those identified retrospectively by the sponosr may be identified and result in multiple adjustments that undermine the statistical validity of any given analysis.*

d. *The endpoint CSUGIE/GDU to a great extent captures symptomatic patients who have UGI pathology that may put them at high risk for a CSUGIE. This new endpoint represents an internal sensitivity analysis for the potential effects of any bias that may be introduced by differences in withdrawal due to UGI adverse events short of CSUGIEs.*

e. *<u>If</u> the results of the diclofenac group are considered to be biased by the differences in withdrawal rates, limiting the study to 6 months does not address the statistical concern adequately. The pattern of withdrawal actually stabilizes over the later period of the study (see table 39.1entitled: "Time to withdrawal due to adverse events: review page 16). One may choose 3,4 or 5 months to limit the bias. Methods other than post hoc elimination of a large portion of the database would need to be considered. Such approaches however are not necessary and would introduce bias.*

Reviewer table 1: Abdominal pain causing withdrawal (%)

| | First six months | | Entire study period | |
	All Subjects	Subjects not on ASA	All subjects	Subjects not on ASA
Celebrex	3.8	3.6	4.3	4.1
Diclofenac	6.1	5.3	6.5	5.8
Ibuprofen	4.5	4.2	4.9	4.7

Source: sponsor tables 42.1, 42.2, 42.4, 42.5

(The results of the study are discussed at greater length later in this review. The sponsor however, defined the final statistical plan with the knowledge that there was a slowing of the event rate at later time points in two of the comparator groups. Sponsor table 14.3(review page 15) indicates that both the ibuprofen and diclofenac groups had a slowing in event rates over time that was not seen in the C group. The ibuprofen group had a dropout rate and GI AE rate much closer to C than to the diclofenac group. The sponsor does not address this issue. Informative censoring due to a higher rate of early withdrawals due to GI AEs in the diclofenac group does not explain the findings over time in the ibuprofen group. One cannot state from the data available why the event rate for C did not follow the pattern seen in both comparator NSAID groups. It is not surprising that event rates fell towards the end of the study for the NSAID comparators. The risk of CSUGIEs associated with NSAIDs has been thought by some to stabilize over the first few months of treatment. Thus, the slowing of event rates over time does not necessarily suggest that a phenomenon was occurring that required the extreme course of changing the original analysis plan.) Table 10.a displays the exposure by drug and time interval. The prominence of exposure to ibuprofen seen in this table in conjunction with the relatively low withdrawal rates (similar to C) seen in table 10.d and the early occurrence of event rates seen in table 14.3 do not support the sponsor's contention that a bias must be sought for the findings in the life table analysis 14.3.
It is plausible that C has a truly higher risk of "late" CSUGIE compared to the "traditional" NSAID comparators.

Table T4-3
Time to Clinically Significant UGI Events - Traditional Definition
Entire Study Period
Log-Rank Test with Censoring Rules Applied

Intent-to-Treat (ITT) Cohort
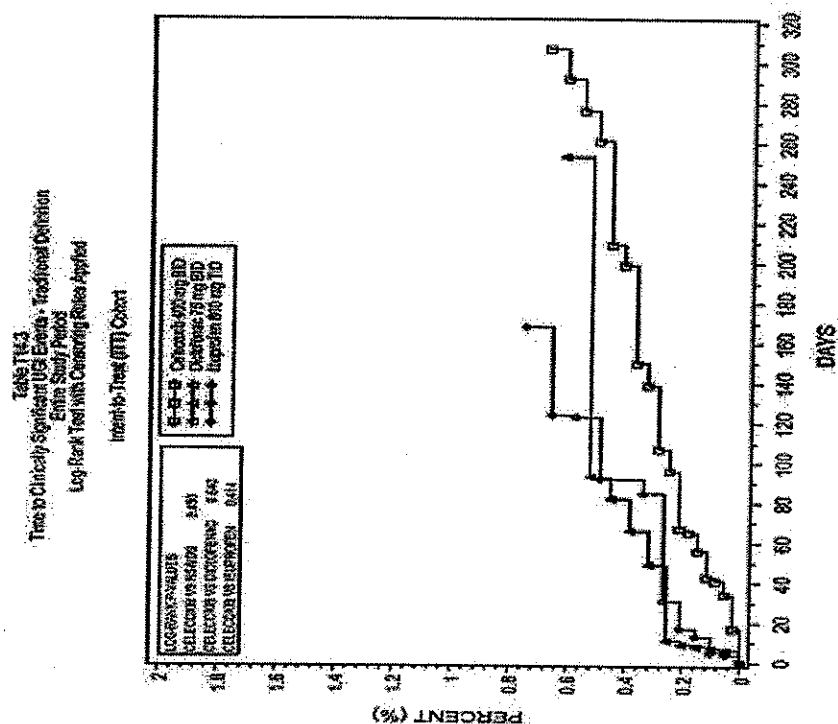
Table 10.a.   Exposure to Treatment Displayed by Interval: Entire Study Period

Interval	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
≤3 mo	1202 (30%)	621 (31%)	715 (36%)
>3 to ≤6 mo	467 (12%)	262 (13%)	246 (12%)
>6 to ≤9 mo	291 (7%)	136 (7%)	130 (7%)
>9 to ≤12 mo	1442 (36%)	913 (46%)	415 (21%)
>12 to ≤15 mo	585 (15%)	64 (3%)	477 (24%)
>15 mo	0 (0)	0 (0)	2 (<1%)

Derived from Table T2.4.1. Entries are No. (%) of patients unless otherwise specified.

B. Rationale for imputation of event rates

The sponsor presented data (table 8.n., review page 18) that suggests that there was informative censoring in the withdrawal of subjects due to GI symptoms. This was presented as the basis for imputing event rates as well as performing an analysis of 6-month data. The sponsor's discussion of this issue is reproduced below.

10. 2. 3. Adverse Events Causing Withdrawal

The most common adverse events causing withdrawal ($\geq 1\%$ in any treatment group) are shown in Table 10.d. Six of the 10 most common events were related to the GI system, five of which represented the most common GI adverse events described above: abdominal pain, dyspepsia, nausea, diarrhea, and flatulence. Three of the events (SGOT increased, SGPT increased, and hepatic function abnormal) were related to elevations in liver function test results, and only led to noteworthy incidences of withdrawals in the diclofenac group. Finally, rash led to withdrawal in more than 1% of patients in the celecoxib and ibuprofen groups, with the highest incidence in the celecoxib group.

The overall incidence of withdrawal due to an adverse event was statistically significantly lower for celecoxib than for diclofenac. Similarly, the differences between celecoxib and diclofenac for three of the GI events (abdominal pain, nausea, and diarrhea) and the three hepatic events (elevations of liver enzyme levels) were statistically significant in favor of

celecoxib. Between celecoxib and ibuprofen, the only statistically significant differences were in diarrhea, gastric ulcer, and rash; for gastric ulcer the difference favored celecoxib.

A comparison of Tables 10.b and 10.d shows that of patients experiencing the five most common GI adverse events, approximately 20% to 30% withdrew as a result. These proportions were similar across the treatment groups.

Other statistically significant differences (at $p \leq 0.05$) occurred between groups in less common GI adverse events leading to withdrawal (Table T42.1). Most of these represented events occurring in very few patients: diverticulosis (0.2% for ibuprofen vs 0.0% for celecoxib); eructation (0.4% for diclofenac vs 0.1% for celecoxib); esophagitis (0.7% for ibuprofen vs. 0.2% for celecoxib); and melena (0.3% for diclofenac vs <0.1% for celecoxib).

Table 10.d.   **Adverse Events Causing Withdrawal with Incidence ≥1% in Any Treatment Group: Entire Study Period**

Adverse Event	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Any event	22.4	26.5 *	23.0
Abdominal pain	4.3	6.5 *	4.9
Dyspepsia	3.8	4.4	3.9
Rash	2.1	0.7 *	1.3 *
Nausea	1.7	2.8 *	1.8
Diarrhea	1.4	2.7 *	0.8 *
Flatulence	1.2	1.8	1.4
Gastric ulcer	0.3	0.7	1.0 *
SGOT increased	0.1	2.1 *	0.1
SGPT increased	0.1	2.3 *	0.1
Hepatic function abnormal	<0.1	1.1 *	<0.1

Derived from Table T42.1. All numbers are percentages of patients unless otherwise specified.
* $p<0.05$ vs celecoxib 400 mg BID.

Table T42.4 shows adverse events leading to withdrawal in the first six months of the study. The incidences in this table are in most cases identical to, or slightly below, those in the entire study period, indicating that almost all patients withdrawing due to adverse events did so within six months of beginning the study. This is illustrated graphically in Table T39.1.

FIGURE 32A4

Time to Withdrawal Due to Adverse Events
Log−Rank Test

Intent−to−Treat (ITT) Cohort

Celecoxib 400 mg BID
Diclofenac 75 mg BID
Ibuprofen 800 mg TID
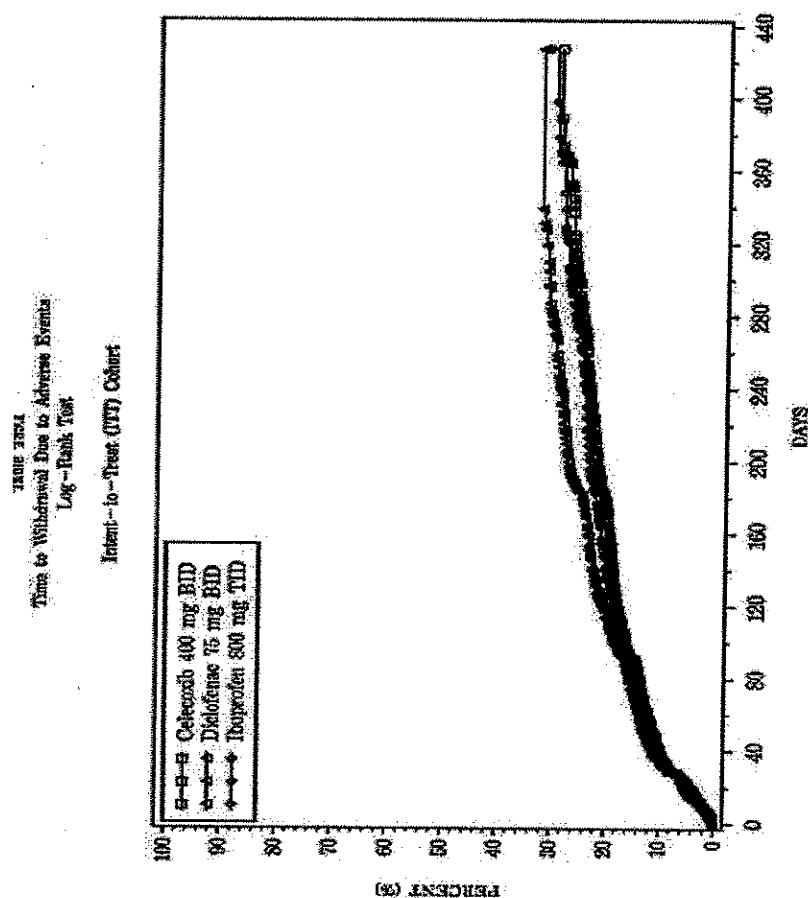
Table 8.n. **Risk Calculation for CSUGIEs and CSUGIEs/GDUs in Patients With and Without GI Symptoms**

	No. with Event/Total	Incidence	Relative Risk
CSUGIEs			
With GI symptoms*	18/1483	1.21%	3.9
Without GI symptoms	20/6485	0.31%	
CSUGIEs/GDUs			
With GI symptoms*	62/1483	4.2%	6.3
Without GI symptoms	43/6485	0.7%	

Derived from Appendix 2.4.17.4.
* Symptoms include moderate to severe abdominal pain, diarrhea, dyspepsia, nausea, or vomiting (the most common GI symptoms).

The data displayed in the sponsor's tables above do not offer compelling evidence to impute an event rate as proposed or confine analysis to the first 6 months. A CSUGIE/ GDU <u>by definition</u> will be associated with a GI symptom.

Upon review of the cases of CSUGIEs in the diclofenac, ibuprofen and C groups it becomes clear that many of the GI symptoms used in the sponsor's calculation of relative risk in fact <u>represented the sentinel symptoms of the CSUGIE</u> and are contemporaneous with the events. Thus, the diarrhea seen in the subjects experiencing a CSUGIE was in fact melena caused by an UGI bleed. This is not surprising, as diarrhea is not a symptom pathophysiologically linked to UGI toxicity. It would therefore not be expected to be a <u>premonitory</u> symptom of a CSUGIE or GDU. The abdominal pain reported by the subjects with CSUGIEs was reported within 24-48 hours of the diagnostic evaluation that identified the endpoint event in most cases. Even if a subject in the study withdrew immediately prior to the ascertainment of an event, the follow-up mandated by the study protocol would have ascertained the event and it would have been included in the analysis. The sponsor has not shown that subjects withdrawing due to abdominal pain or diarrhea prior to an event would have been at a higher risk than those remaining in the study.

<u>A review of the CSUGIEs database reveals that only 2/38 (5%) of subjects that experienced CSUGIEs had abdominal pain over the month prior to event. This finding is consistent with a body of literature that suggests that complicated NSAID related ulcers are not associated with prior symptoms.[10]</u>

Thus the sponsor has not provided adequate support for the hypothesis of informative censoring as well as an adequately justified statistical imputation.

C. Combined analysis of CSUGIEs and GDUs.

The inclusion of <u>a combined</u> analysis of CSUGIEs and GDU was a post-hoc decision. Analysis of symptomatic ulcers identified during the study was prespecified as an endpoint of interest in the protocol. This combined analysis produces an endpoint that is most appropriately described as "symptomatic ulcer". The current GI warning on NSAID labels uses the term "PUB (perforation, ulcer, bleed)" to describe the GI events widely described in the medical literature at the time of the development of this section of NSAID labels. This acronym in fact defines a symptomatic ulcer. Such a term does define a clinically relevant endpoint. It represents ulcers identified during an evaluation of patients experiencing symptoms serious enough to warrant physician intervention. Such an event must by definition be relevant to the patient. There are several difficulties with this endpoint as the <u>primary endpoint</u> of study in a controlled trial (aside from the lack of prespecification of this composite endpoint and the attendant issues of statistical multiplicity).

a. *Many patients on NSAIDs including C experience UGI symptoms that are consistent with ulcer symptoms that in fact are not related to ulcers. Up to 50% of patients on NSAIDs experience dyspepsia. Up to 15% discontinue therapy due to such symptoms.[2] Only a fraction of these patients have ulcers on UGI endoscopy. Thus, there are a significant number of patients who will have GDUs on endoscopy without causal association to symptoms. The rate of such events would be even higher in a clinical trial where protocol driven ascertainment or bias within the clinical trial setting identifies ulcers that would not be identified in clinical practice. Patients without alarm symptoms on NSAIDs are generally taken off presumed offending medication without any further sequel. Therefore the use of the endpoint PUB in a clinical trial introduces a somewhat artificial entity that does not have the degree of clinical relevance that is inherent in the more clearly defined endpoint, CSUGIE or "POB" (perforation, obstruction or bleed."*

b. *Symptomatic ulcers, whether clinically or protocol derived do not represent the same severity of endpoint as a CSUGIE. Only a small fraction of ulcers are thought to result in a clinically serious outcome. In the original NDA database for C the vast majority of ulcers identified were protocol derived and not related to any symptoms. A composite outcome should contain endpoints with similar clinical importance. The correlation between symptomatic ulcers and ulcers that are serious is too weak to consider the two in the same endpoint of a prospective study. The current NSAID warning used the endpoint "PUB" due to the limitation of the available data at the time of conception. This endpoint would not be an appropriate composite endpoint to be studied prospectively. Symptomatic ulcers are so much more common that CSUGIEs that the outcome would be primarily determined by the symptomatic ulcer results and therefore are most accurately defined as such, unless subanalysis of CSUGIEs indicates that this element independently shows a meaningful difference in rates among any chosen comparators. Separate analyses of CSUGIEs and symptomatic ulcers allow for a more meaningful and accurate interpretation of results. The lower rates anticipated for the CSUGIEs reduce statistical power of any trial. If trends are similar for both endpoints and surrogacy is felt to be strongly supported, conclusion about CSUGIEs may be considered based on the totality of evidence from both endpoint analyses.*

D. Subanalysis based on aspirin use

Subanalysis based on aspirin use is appropriate. The lack of prespecification creates problems if the primary hypothesis of the study is not supported by the results. Safety data on C or any NSAID when used with and without concomitant aspirin is clinically important information. If concomitant aspirin negates any benefit of a COX-2 selective

agent, public health and health economics have been meaningfully informed. Likewise, additive GI, renal or other systemic risks increased by concomitant use would be vital

information for physicians and patients. One strength of this study was in the inclusion of the 20% of otherwise eligible patients who were on aspirin for cardiovascular protection. This issue has been discussed previously in the inclusion criteria review section. Therefore, if statistical adjustment can be made, this subgroup is biologically based and clinically informative.

Summary comments on statistical plan

1. *The final statistical plan that included the multiple subanalyses reviewed above produces serious multiplicity issues that the sponsor has not addressed. There are 34 comparisons possible based on three comparators and stratification based on study duration, aspirin use and definition of the endpoint of interest (CSUGIE and CSUGIE/GDU). There is good rationale for statistical analysis of subgroups based on the use of aspirin. Statistical adjustment however is necessary due to the multiple comparisons introduced by this analysis.*

2. *The sponsor has not adequately justified the value of an analysis limited to 6-month data nor adequately justified replacing the original analysis with this post hoc analysis. The importance of chronic exposure data to the safety assessment of a drug is noted.*

3. *Analysis of ulcers identified based on symptoms during a clinical trial (PUBs) are anticipated to overestimate such events in practice, however, comparative rates are meaningful. Combining CSUGIEs and the symptomatic GDUs into a single endpoint (PUB) is appropriate and meaningful only if they independently are associated with meaningful comparative results.*

4. *This reviewer considers imputation of an event rate for the diclofenac group based on the analysis presented by the sponsor to be unsupported. The relative risk used for this analysis was based on symptoms that in fact were part of and simultaneous with the outcome event presentation. The imputation method is therefore tautological/circular.*

Study results:

As noted previously, after the study ended the sponsor added a new set of analyses that was based on the first six months of study instead of the entire study period. (This additional analysis is **superimposed** upon a decision to end the study before the prespecified number of CSUGIEs had been reached. The early termination was based on the slowing of the event rate over time and a high cumulative drop out rate. No statistical penalty was applied to the early termination, following discussion with the division, as no interim analysis was performed.)

Reviewer's comment: The most clinically relevant analysis covers the complete study period as specified in the original protocol. An artificial definition of 6 months is not based on clinical practice in prescribing medications for arthritis. One must assume that chronic therapy will extend beyond 6 months and therefore safety endpoints for the full length of the study are most relevant. The original study period was predefined for statistical reasons. Assumptions regarding statistical significance are based on pre-specification of study period. Therefore, the primary analysis is the analysis considered to be most statistically conclusive. The six-month analysis will be reviewed only as a potentially supportive analysis.

Patient Disposition
The patient disposition database was reviewed:
386 investigators were recruited in The United States and Canada. Only 4 centers contributed more than one CSUGIE. No site contributed more than 2 events and the enrollment was well distributed among the centers reporting events.

Database audit:
A review of approximately 50 % of the cases referred to the adjudication committee revealed no CSUGIEs that appeared to be missed. The cases adjudicated as CSUGIEs were well documented. No meaningful differences were identified between the committee's adjudication decisions and this reviewer's assessment based on the pre-specified definition of a CSUGIE.

Demographics:

Sponsor tables T3, T6, T7, T8 and T10 indicates no significant differences in age, gender, race, history of UGI bleed, GDU (gastroduodenal ulcers), cardiovascular disease and serologic evidence of H. pylori infection (past or current), duration of disease, tobacco use anti-coagulant use, aspirin use and steroid use. Table T7 indicates a potentially meaningful difference in alcohol use. Most of the excess in the diclofenac group was in the category of 1 drink or less per day. This low intake of alcohol is unlikely to create a meaningful impact on the outcome. Alcohol is not considered to be a strong risk factor for CSUGIEs. Sponsor table 25.2 supports this interpretation by revealing an inconsistent relationship between the variable of alcohol intake and CSUGIE outcomes.

Table T25.2
Risk Factor Analysis of Clinically Significant UGI Events (Medication, Alcohol, and Tobacco Use)

Intent-to-Treat (ITT) Cohort

	Celecoxib 400 mg BID (N = 3987)		Diclofenac 75 mg BID (N = 1996)		Ibuprofen 800 mg TID (N = 1985)		P-Value [a]	
							Treatment by Factor Interaction	Factor Effect
CORTICOSTEROID USE								
ANY	3/1219	0.2%)	2/ 568(	0.4%)	2/ 607|	0.3%)	0.994	0.046
NONE	14/2765|	0.5%)	8/1428(	0.6%)	9/1378|	0.7%)		
P-VALUE(b)	0.171		0.503		0.276			
ASPIRIN USE								
ANY	9/ 882|	1.0%)	6/ 445(	1.3%)	1/ 412|	0.2%)	0.020	0.006
NONE	6/3105|	0.3%)	4/1551(	0.3%)	10/1573|	0.6%)		
P-VALUE(b)	0.005		0.010		0.335			
ALCOHOL USE								
ANY	4/1232|	0.3%)	5/ 812(	0.6%)	4/ 386(	1.0%)	0.326	0.605
NONE	13/2753|	0.5%)	5/1184(	0.4%)	7/1599|	0.4%)		
P-VALUE(b)	0.506		0.574		0.166			
TOBACCO USE								
ANY	0/ 629|	0.0%)	2/ 311(	0.6%)	0/ 284|	0.0%)	0.057	0.059
NONE	17/3356|	0.5%)	8/1685(	0.5%)	11/1701|	0.6%)		
P-VALUE(b)	0.993		0.657		0.992			
ANTICOAGULANT USE								
ANY	0/ 43|	0.0%)	0/ 24(	0.0%)	0/ 20|	0.0%)	1.000	0.339
NONE	17/3945|	0.4%)	10/1972(	0.5%)	11/1965|	0.6%)		
P-VALUE(b)	0.993		0.994		0.991			

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

Table T 6 suggests a potentially significant difference between diclofenac and the other two comparators in baseline history of GI-related NSAID intolerance. Although a difference of 1.4-1.8% is small, the sponsor has identified a similar differential in withdrawal due to a sponsor-generated definition of GI adverse events as critical to the interpretation of the study. This demographic data may be relevant to the results if NSAID intolerance (independent of a history of CSUGIE/DU) is a risk factor form CSUGIEs.

Table T3
Baseline Demographic Characteristics

Intent-to-Treat (ITT) Cohort

	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)	P-value	
AGE (yrs)				0.011 *	(a)
N	3987	1996	1985		
Mean	60.6	60.1	59.5		
SD	11.66	11.99	11.93		
Median	61.0	61.0	60.0		
Range	20- 89	21- 90	18- 90		
<= 34	76 (1.9%)	52 (2.6%)	49 (2.5%)		
35 - 44	272 (6.8%)	166 (8.3%)	172 (8.7%)		
45 - 54	881 (22.1%)	404 (20.2%)	458 (23.1%)		
55 - 64	1199 (30.1%)	612 (30.7%)	582 (29.3%)		
65 - 74	1072 (26.9%)	526 (26.4%)	507 (25.5%)		
>= 75	487 (12.2%)	236 (11.8%)	217 (10.9%)		
GENDER				0.064	(b)
Male	1255 (31.5%)	650 (32.6%)	580 (29.2%)		
Female	2732 (68.5%)	1346 (67.4%)	1405 (70.8%)		
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)		
RACE/ETHNIC ORIGIN				0.001 ***	(b)
Caucasian	3528 (88.5%)	1784 (89.4%)	1713 (86.3%)		
Black	301 (7.5%)	151 (7.6%)	172 (8.7%)		
Asian	29 (0.7%)	19 (1.0%)	9 (0.5%)		
Hispanic	107 (2.7%)	36 (1.8%)	75 (3.8%)		
Other	22 (0.6%)	6 (0.3%)	16 (0.8%)		
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)		

Table T6
GI Risk Factors

Intent-to-Treat (ITT) Cohort

HISTORY OF:	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)	P-value (a)
UPPER GI BLEEDING				0.695
Yes	68 (1.7%)	30 (1.5%)	28 (1.4%)	
No	3919 (98.3%)	1966 (98.5%)	1957 (98.6%)	
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)	
GASTRODUODENAL ULCER				0.503
Yes	334 (8.4%)	170 (8.5%)	151 (7.6%)	
No	3653 (91.6%)	1826 (91.5%)	1834 (92.4%)	
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)	
GI-RELATED NSAID INTOLERANCE (b)				0.098
Yes	347 (8.7%)	202 (10.1%)	165 (8.3%)	
No	3640 (91.3%)	1794 (89.9%)	1820 (91.7%)	
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)	
CARDIOVASCULAR DISEASE				0.978
Yes	1602 (40.2%)	805 (40.3%)	794 (40.0%)	
No	2384 (59.8%)	1190 (59.6%)	1190 (59.9%)	
TOTAL	3986 (100.0%)	1995 (99.9%)	1984 (99.9%)	
FLEXSURE FOR H. PYLORI				0.743
Negative	2448 (61.4%)	1243 (62.3%)	1213 (61.1%)	
Positive	1536 (38.5%)	752 (37.7%)	769 (38.7%)	
TOTAL	3984 (99.9%)	1995 (99.9%)	1982 (99.8%)	

The trend towards higher percentage of enrollees with a history of GI-related NSAID intolerance should be analyzed further. Sponsor table 24.2 suggests that there is a two-fold or greater risk of a CSUGIE in subjects with a history of GI-related NSAID intolerance. The same trend is seen in the outcomes for CSUGIE/GDU displayed in table 24.3 One may consider an adjustment of rates based on the imbalance in baseline demographics for this variable. This would result in a lower rate for the diclofenac group. Such an adjustment is not suggested.

Table T24.2
Risk Factor Analysis of Clinically Significant UGI Events (GI History)

Intent-to-Treat (ITT) Cohort

	Celecoxib 400 mg BID (N = 1987)	Diclofenac 75 mg BID (N = 1996)	Ibuprofen 800 mg TID (N = 1985)	P-Value (a) Treatment by Factor Interaction	Factor Effect
HISTORY OF UPPER GI BLEEDING					
YES	1/ 68 1.5%	0/ 30 0.0%	2/ 28 7.1%		
NO	16/3919 0.4%	10/1966 0.5%	9/1957 0.5%	0.207	0.017
P-VALUE(b)	0.144	0.904	<0.001		
HISTORY OF GASTRODUODENAL ULCER					
YES	2/ 334 0.6%	4/ 170 2.6%	1/ 151 0.7%		
NO	15/3653 0.4%	6/1826 0.3%	10/1834 0.3%	0.185	0.030
P-VALUE(b)	0.509	0.202	0.762		
HISTORY OF UPPER GI BLEEDING OR GASTRODUODENAL ULCER					
YES	2/ 365 0.6%	4/ 180 2.2%	2/ 162 1.2%		
NO	15/3624 0.6%	6/1616 0.3%	9/1823 0.5%	0.263	0.012
P-VALUE(b)	0.554	0.003	0.183		
HISTORY OF GI-RELATED NSAID INTOLERANCE					
YES	3/ 347 0.9%	2/ 202 1.0%	2/ 165 1.2%		
NO	14/3640 0.4%	8/1794 0.4%	9/1820 0.5%	0.993	0.055
P-VALUE(b)	0.163	0.272	0.222		
HISTORY OF CARDIOVASCULAR DISEASE					
YES	14/1602 0.9%	7/ 805 0.9%	4/ 796 0.5%		
NO	3/2384 0.1%	3/1190 0.3%	7/1190 0.6%	0.036	<0.001
P-VALUE(b)	0.002	0.566	0.793		
PLEXSURE FOR H. PYLORI					
POSITIVE	5/1536 0.3%	5/ 752 0.7%	7/ 763 0.9%		
NEGATIVE	12/2448 0.5%	5/1243 0.4%	4/1213 0.3%	0.176	0.385
P-VALUE(b)	0.460	0.437	0.092		

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

Table T24.1
Risk Factor Analysis of Clinically Significant UGI Events or GD Ulcer (GI History) - NSAIDs Pooled

Intent-to-Treat (ITT) Cohort

	Celecoxib 400 mg BID (N = 3987)	NSAIDs (N = 3981)	P-Value (a) Treatment by Factor Interaction	Factor Effect
HISTORY OF UPPER GI BLEEDING				
YES	3/ 68(4.4%)	3/ 58(5.2%)	0.751	0.003
NO	40/3919(1.0%)	59/3923(1.5%)		
P-VALUE(b)	0.006	0.013		
HISTORY OF GASTRODUODENAL ULCER				
YES	9/ 334(2.7%)	12/ 321(3.7%)	0.921	<0.001
NO	34/3653(0.9%)	50/3660(1.4%)		
P-VALUE(b)	0.002	<0.001		
HISTORY OF UPPER GI BLEEDING OR GASTRODUODENAL ULCER				
YES	10/ 352(2.8%)	14/ 342(4.1%)	0.599	<0.001
NO	33/3634(0.9%)	48/1639(1.3%)		
P-VALUE(b)	<0.001	<0.001		
HISTORY OF GI-RELATED NSAID INTOLERANCE				
YES	10/ 347(2.9%)	10/ 367(2.7%)	0.348	<0.001
NO	33/3640(0.9%)	52/3614(1.4%)		
P-VALUE(b)	0.001	0.037		
HISTORY OF CARDIOVASCULAR DISEASE				
YES	27/1602(1.7%)	32/1599(2.0%)	0.232	<0.001
NO	16/2384(0.7%)	30/2380(1.3%)		
P-VALUE(b)	0.002	0.048		
FLEXSURE FOR H. PYLORI				
POSITIVE	19/1536(1.2%)	34/1521(2.2%)	0.335	0.008
NEGATIVE	24/2448(1.0%)	28/2456(1.1%)		
P-VALUE(b)	0.423	0.005		

(a) Based on survival analysis on the time to UGI events with a COX proportional hazards model.
(b) Within group survival analysis on the time to UGI events with a COX proportional hazards model.

Table T7
Baseline Alcohol and Tobacco Use

Intent-to-Treat (ITT) Cohort

HISTORY OF:	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)	P-value (a)
ALCOHOL USE				<0.001 ***
None	2751 (69.0%)	2164 (59.3%)	1599 (80.6%)	
Yes (b)	1232 (30.9%)	812 (40.7%)	386 (19.4%)	
1 or Fewer Drinks per Day	1079 (27.1%)	712 (35.7%)	326 (16.4%)	
2-3 Drinks per Day	130 (3.3%)	93 (4.7%)	46 (2.3%)	
4 or More Drinks per Day	11 (0.3%)	7 (0.4%)	2 (0.1%)	
Yes - No Specification	12 (0.3%)	0 (0.0%)	12 (0.6%)	
TOTAL	3985 (99.9%)	1996 (100.0%)	1985 (100.0%)	
TOBACCO USE (c)				0.314
None	3356 (84.2%)	1685 (84.4%)	1701 (85.7%)	
Yes (b)	629 (15.8%)	311 (15.6%)	284 (14.3%)	
Level I	298 (8.0%)	100 (5.0%)	62 (3.1%)	
Level II	229 (5.7%)	152 (7.6%)	75 (3.8%)	
Level III	85 (2.1%)	59 (3.0%)	30 (1.5%)	
Yes - No Specification	116 (2.9%)	0 (0.0%)	117 (5.9%)	
TOTAL	3985 (99.9%)	1996 (100.0%)	1985 (100.0%)	

Table T8
Arthritis History - Primary Diagnosis

Intent-to-Treat (ITT) Cohort

	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)	P-value (a)
OA DURATION (yrs)				0.885
N	2875	1447	1424	
Mean	10.25	10.35	9.94	
SD	9.702	10.330	9.447	
Median	8.00	7.00	7.17	
Range	0.2- 64.0	0.3- 95.0	0.3- 64.0	
RA DURATION (yrs)				0.215
N	1089	543	551	
Mean	11.25	10.47	10.87	
SD	9.859	9.377	9.807	
Median	9.00	8.00	8.00	
Range	0.0- 56.0	0.3- 57.0	0.0- 57.0	

Table T10
GI Risk Factors - Medication Use

Intent-to-Treat (ITT) Cohort

	Celecoxib 400 mg BID (N=3987)	Diclofenac 75 mg BID (N=1996)	Ibuprofen 800 mg TID (N=1985)	P-value (a)
CORTICOSTEROID USE				0.357
None	2766 (69.4%)	1428 (71.5%)	1378 (69.4%)	
One Dose to <10% Study Days	413 (10.4%)	183 (9.2%)	214 (10.8%)	
>=10% Study Days	806 (20.2%)	385 (19.3%)	393 (19.8%)	
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)	
ANTICOAGULANT USE				0.348
None	3945 (98.9%)	1972 (98.8%)	1965 (99.0%)	
One Dose to <10% Study Days	24 (0.6%)	8 (0.4%)	8 (0.4%)	
>=10% Study Days	18 (0.5%)	16 (0.8%)	12 (0.6%)	
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)	
ASPIRIN USE				0.541
None	3105 (77.9%)	1551 (77.7%)	1573 (79.2%)	
One Dose to <10% Study Days	196 (4.9%)	104 (5.2%)	83 (4.2%)	
>=10% Study Days	686 (17.2%)	341 (17.1%)	329 (16.6%)	
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)	
ASPIRIN USE DURING FIRST SIX MONTHS				0.198
None	3154 (79.1%)	1567 (78.5%)	1602 (80.7%)	
Any	833 (20.9%)	429 (21.5%)	383 (19.3%)	
TOTAL	3987 (100.0%)	1996 (100.0%)	1985 (100.0%)	

Conclusion to demographics section:

1. *There was an imbalance in the percent of subjects drinking three or fewer alcohol containing beverages per day. This is not expected to impact on the results significantly. Any bias introduced by this imbalance would be expected to result in a slightly higher event rate in the diclofenac group.*
2. *A higher baseline rate of GI-related NSAID intolerance was seen in the diclofenac group compared to the C and ibuprofen groups. This difference may slightly impact on the withdrawals in this group. It is clear that there are potential confounding variables that are not completely accounted for in the original analysis. It is also clear that selectively choosing which variables to use in imputing rates introduces a bias as well.*
   Such potential effects should be considered when assessing the sponsor's proposed imputed event rate for the diclofenac group.
3. *There was no meaningful difference in the baseline histories for the other potentially relevant risk factors.*

Disposition:

Sponsor figure 7.b. displays the disposition over the course of the study.

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Figure 7.b.   Disposition of Patients: Entire Study Period

```
                        ┌─────────────────────────┐
                        │      N = 8059           │
                        │  Patients Randomized    │
                        └─────────────────────────┘
                                    │
                        ┌─────────────────────────┐
                        │      N = 7968           │
                        │ Patients Taking Study   │
                        │      Medication         │
                        └─────────────────────────┘
                                    │
          ┌─────────────────────────┼─────────────────────────┐
  ┌───────────────┐        ┌───────────────┐         ┌───────────────┐
  │   N = 3987    │        │   N = 1996    │         │   N = 1985    │
  │  Celecoxib    │        │  Diclofenac   │         │  Ibuprofen    │
  │  400 mg BID   │        │  75 mg BID    │         │  800 mg TID   │
  └───────────────┘        └───────────────┘         └───────────────┘
          │                        │                         │
  ┌───────────────┐        ┌───────────────┐         ┌───────────────┐
  │   N = 1779    │        │   N = 939     │         │   N = 691     │
  │  Completed    │        │  Completed    │         │  Completed    │
  │    Study      │        │    Study      │         │    Study      │
  └───────────────┘        └───────────────┘         └───────────────┘
```

N = 2208 Withdrawn	N = 1057 Withdrawn	N = 1294 Withdrawn
Lost to follow-up: 0	Lost to follow-up: 0	Lost to follow-up: 0
Preexisting violation: 27	Preexisting violation: 11	Preexisting violation: 12
Protocol noncompliance: 585	Protocol noncompliance: 197	Protocol noncompliance: 365
Treatment failure: 691	Treatment failure: 309	Treatment failure: 456
Adverse event: 905	Adverse event: 540	Adverse event: 461

```
                        ┌─────────────────────────┐
                        │      N = 3409           │
                        │ Patients Completing     │
                        │       Study             │
                        └─────────────────────────┘
```

Derived from Tables T1 and T2.3. Patients counted as completing the study either completed the full scheduled treatment period or remained in the study at the time of study closure.

Table 10d displays withdrawal rates related to GI adverse events that the sponsor has proposed may be relevant to subsequent risk of CSUGIEs.

Table 10.d.   Adverse Events Causing Withdrawal with Incidence ≥1% in Any Treatment Group: Entire Study Period

Adverse Event	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Any event	22.4	26.5 *	23.0
Abdominal pain	4.3	6.5 *	4.9
Dyspepsia	3.8	4.4	3.9
Rash	2.1	0.7 *	1.3 *
Nausea	1.7	2.8 *	1.8
Diarrhea	1.4	2.7 *	0.8 *
Flatulence	1.2	1.8	1.4
Gastric ulcer	0.3	0.7	1.0 *
SGOT increased	0.1	2.1 *	0.1
SGPT increased	0.1	2.3 *	0.1
Hepatic function abnormal	<0.1	1.1 *	<0.1

Derived from Table T42.1. All numbers are percentages of patients unless otherwise specified.
* $p < 0.05$ vs celecoxib 400 mg BID.

Tables 37.1, 38.1 and 39.1 suggest a clinically marginal difference overall in drop out rates among the three comparators. These tables in a crude way suggest that the comparators represented appropriate choices for drugs with similar overall tolerability.
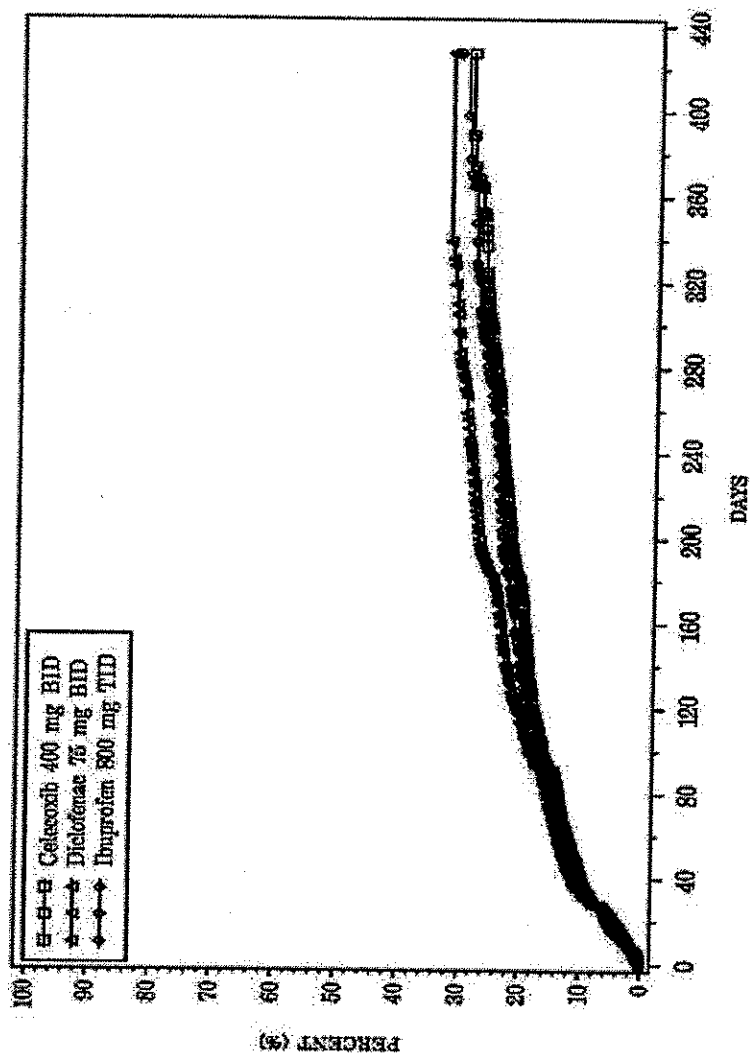
Table TS71
Time to Withdrawal Due to Lack of Arthritis Efficacy
Log-Rank Test

Intent-to-Treat (ITT) Cohort
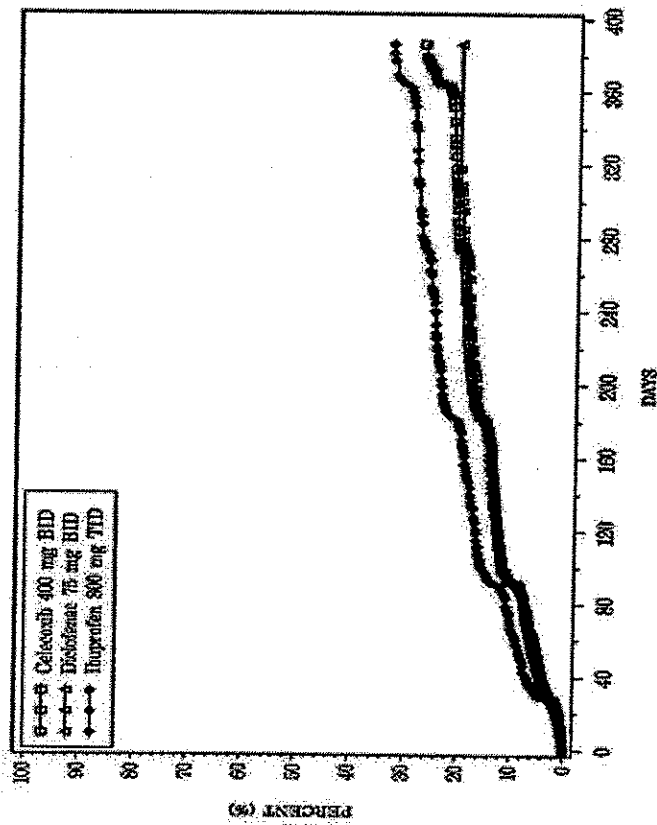
Legend:
Celecoxib 400 mg BID
Diclofenac 75 mg BID
Ibuprofen 800 mg TID

Table T331
Time to Withdrawal Due to Adverse Events
Log-Rank Test

Intent-to-Treat (ITT) Cohort

Table 7.5.8.1
Time to Withdrawal Due to Lack of Arthritis Efficacy or Adverse Event
Log-Rank Test

Intent-to-Treat (ITT) Cohort
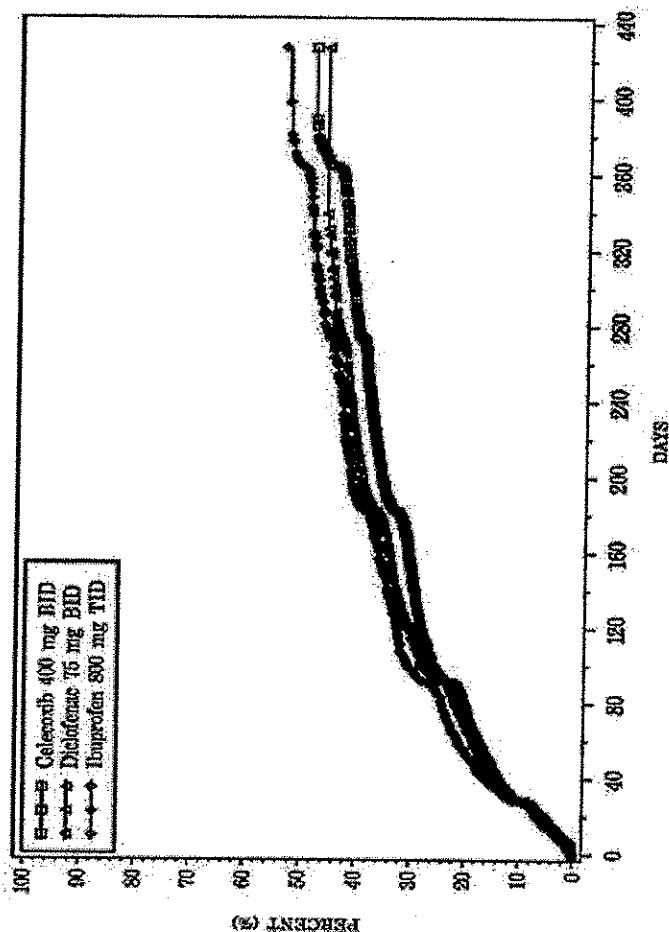
Protocol violations:

Table 7.a.   Distributions of Inclusion/Exclusion Criteria Violation by
              Treatment Group

Inclusion/Exclusion Criterion	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
Inclusion #2: Negative pregnancy test ≤7 days before first dose	-	1	1
Inclusion #6: Written informed consent prior to study procedures	-	1	-
Exclusion #1: Active malignancy or history of malignancy	5	1	4
Exclusion #3: Active GI disease	2	1	1
Exclusion #4: History of gastroduodenal surgery	6	2	4
Exclusion #5: Clinically significant renal, hepatic, or coagulation dysfunction	-	1	-
Exclusion #6: ALT or AST ≥1.5x ULN or other clinically significant laboratory abnormality	8	5	6
Exclusion #7: Positive fecal occult blood test at screening	15	3	5
Exclusion #8: Hypersensitivity to sulfonamides, COX-2 inhibitors, diclofenac, or ibuprofen	10	6	7
Exclusion #10: Enrollment in prior celecoxib study	1	1	1

Derived from Appendices 4.1.1 and 4.1.2. Entries are numbers of patients.

When normalized for enrollment numbers, there were no significant differences in withdrawal due to inclusion/exclusion criterion violation.

GI ENDPOINT RESULTS

The sponsor submitted multiple analyses in the CSR that are listed below. Given the existence of prespecified analyses that identified a primary endpoint success (statistical superiority of C over the combined NSAID comparators and subsequent statistical comparison of C to each individual NSAID comparator at the end of the study period): meaningful interpretation of additional statistical analyses is difficult without statistical adjustment. Any possible meaningful additional analysis requires acceptance of a rationale for the analysis and a statistical correction. This issue was discussed previously in this review within the section on statistical methods. The following analyses will be reviewed.

1. *Primary prespecified analysis: CSUGIE (traditional definition), entire ITT as well as subgroups based on low dose aspirin ($\geq$325mg/day) use for the entire study period*

2. *Primary prespecified analysis: CSUGIE (alternate definition), entire ITT as well as subgroups based on low dose aspirin ($\geq$325mg/day) use for the entire study period*

3. *Secondary analysis: CSUGIE/GDU, entire ITT as well as subgroups based on low dose aspirin ($\geq$325mg/day) use for the entire study period*

CSUGIE Results:

The reader is referred to appendix I for the definition of CSUGIEs and the methods of ascertainment of CSUGIEs and GDUs.

Table 8.f. **Summary of CSUGIE Incidence: Traditional Definitions - Entire Study Period**

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celecoxib Vs:		
				Diclo	Ibu	Both
All Patients						
	n=3987	n=1996	n=1985			
No. of CSUGIEs						
Uncensored	17	10	11			
Censored	3	1	2			
Total	20	11	13			
Week 52 crude rate†	0.43%	0.50%	0.55%	0.640	0.414	0.450
No. per 100 pt-yrs†	0.73	0.93	0.98			
Patients not Taking Aspirin						
	n=3105	n=1551	n=1573			
No. of CSUGIEs						
Uncensored	8	4	10			
Censored	1	0	1			
Total	9	4	11			
Week 52 crude rate†	0.26%	0.26%	0.64%	0.972	0.037	0.185
No. per 100 pt-yrs†	0.44	0.48	1.14			

Derived from Tables T14.1 through T15.3.
† Censoring rule applied.

Table 8.e.   **Distributions of CSUGIEs by Category: Traditional Definitions - Entire Study Period**

Event Category	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
UGI Bleeding (Category 1)			
1A: Hematemesis with ulcer/large erosion	1	-	-
1B: Ulcer/large erosion with evidence of bleeding	8	4	7
1C: Melena with ulcer/large erosion	5 *	4	3 *
1D-1: Hemoccult-positive stool with ulcer/large erosion and hematocrit/hemoglobin drop	3 †	2	3
1D-2: Hemoccult-positive stool with ulcer/large erosion and orthostasis	-	-	-
1D-3: Hemoccult-positive stool with ulcer/large erosion and transfusion	-	-	-
1D-4: Hemoccult-positive stool with ulcer/large erosion and blood in stomach	-	-	-
UGI Perforation (Category 2)	1	1 †	-
Gastric Outlet Obstruction (Category 3)	2	-	-
Total	20	11	13
Total Uncensored	17	10	11

Derived from Table T16 and Appendix 2.6.1. Entries are numbers of patients. See Section 6. 4. 3. 1. for full definitions.
* Two of these events censored from primary analysis. † One of these events censored.
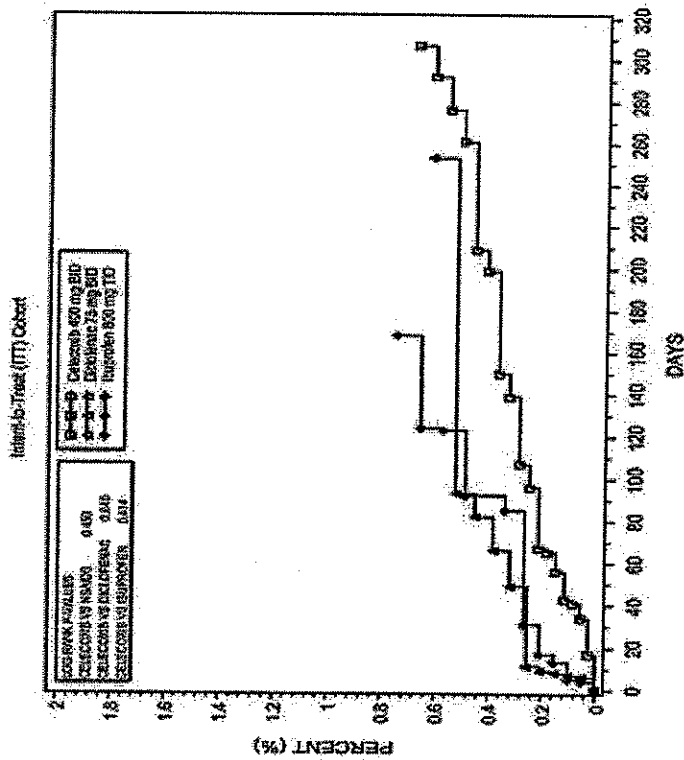
*Table 8.f. indicates that there is no statistically significant difference between Celebrex
and the NSAID group at the primary prespecified endpoint: Celebrex vs. NSAIDs
combined for the entire study period, all subjects ITT population.*

*If one were to bypass the statistical hierarchy and compare Celebrex to each NSAID
separately, the 52-week rate suggests a trend in favor of ibuprofen (22% reduction in
CSUGIE rate) that may be clinically meaningful if validated. The trend in favor of
diclofenac (14% reduction in CSUGIE rate) would be of less clear clinical meaning if
validated.*

*Table 14.3 displays the events over time. There is a relatively steady event rate seen in
the C group while both ibuprofen and diclofenac display a slowing in the rate of accrual
of events over time. This table suggests that long term there may be a higher event rate
associated with the use of C compared to the other two comparators. The similarity in
pattern seen for both ibuprofen and diclofenac do not support the sponsor's imputation of
a higher rate for the diclofenac group based on a higher withdrawal rate due to GI AEs.
The ibuprofen group experienced the same drop off in event rates even before 6 months
without any difference compared to C in withdrawal due to GI AEs. The same pattern is
seen in table 15.3, which displays the time to event for the subgroup of subjects not taking
aspirin. This trend is worrisome.*

*As noted earlier in this review, the inclusion of aspirin users in this study was
encouraged by the Agency. Important safety information has been collected in a large
extended use outcome study that approximates the anticipated population of patients who
may be exposed to C. Therefore further analysis is appropriate based on the known
biologic effects of aspirin on the UGI tract. It was anticipated from the outset that 10-
20% of subjects would be on low dose aspirin and confound the outcome in those
subjects. Therefore, it is clinically relevant to consider the results in subjects on aspirin
and not on aspirin. The results of such an subanalysis reveals no statistically significant
difference between Celebrex and the NSAID comparators combined, which was the
prespecified comparison. A further subanalysis by individual NSAID reveals no trend for
C versus diclofenac and a strong nominal trend for the C versus ibuprofen comparison.
The p-value of .037 is uncorrected for multiple comparisons.*

*If validated, these results would be of little support for a generalizable statement
regarding the safety advantage of Celebrex over traditional NSAIDs as a class. Such
validation would confirm current opinion that there is a spectrum of GI toxicity among
NSAIDs. It would place C within this spectrum rather than distinctly outside the
spectrum. This statement has profound impact on the interpretation of safety comparisons*

of other COX-2 agents as well. Choice of a more toxic comparator for a GI safety study may not be used to extrapolate to the universe of "traditional" less selective COX inhibitors (NSAIDs).

Sponsor table 8.e. displays the results by type of CSUGIE. These results corroborate the clinical predominance of bleeding in the toxicity of NSAIDs in the upper GI tract. These results also identify within a well-controlled study the most common presentations for such bleeding events. The general presentation of CSUGIEs in the C group was similar to that seen in the traditional NSAID group.

CSUGIE/GDU Results

Sponsor table 8.k. displays the results of an analysis that was not prespecified: the event commonly referred to as a "PUB". This endpoint is discussed earlier in this review and does represent a clinically relevant endpoint. One would expect that trends would be similar between this endpoint and the more rigorous endpoint of CSUGIEs. While the surrogacy of ulcers in relation to CSUGIEs has not been fully validated, a trend was suggested in the original NDA database submitted in 1998. The MUCOSA trial[5] (a trial assessing the impact of misoprostol on the rate of PUBs) also suggests a correlation between rates of endoscopic ulcers and rates of CSUGIEs for NSAIDs as a group when bridged to endoscopic trials that evaluated the impact of misoprostol on the rates of asymptomatic endoscopic ulcers.

Overall, the trends are similar in this analysis compared to the clinically more significant endpoints of CSUGIE (traditional). There is a strong trend in favor of C compared to ibuprofen in subjects not taking aspirin with no trend between C compared to diclofenac. In fact the results show a nominally lower CSUGIE/GDU rate in the diclofenac group compared to C in subjects not taking concomitant aspirin.

As discussed previously in this review, the CSUGIE/GDU analysis informs the interpretation of the sponsor's post hoc imputation of event rates for the diclofenac group based on a high drop out rate for GI adverse events. The protocol mandated that clinically relevant symptoms be evaluated in the study patients. Those episodes of symptoms severe enough to warrant withdrawal should have, to a great extent been referred for evaluation. UGI mucosal lesions (ulcers) that may be interpreted as relevant to future risk of a CSUGIE would have been ascertained and thus have been reflected in the CSUGIE/GDU data (PUB). The CSUGIE/GDU results should be relatively free of potential bias related to inform censoring based on withdrawal due to GI-related adverse events. The lack of significant differentiation between diclofenac and C in this endpoint is consistent with the primary endpoint analysis (CSUGIE for the entire study period) and argues strongly against the sponsor's claim of informative censoring driving the negative results vis a vis the diclofenac-C comparisons. The results of the comparison between C and ibuprofen also support the primary analysis.

Table 8.k. **Summary of CSUGIE/GDU Incidence: Traditional Definitions - Entire Study Period**

	Celecoxib 400 mg BID	Diclofenac 75 mg BID	Ibuprofen 800 mg TID	Log-Rank P Values for Celecoxib Vs:	
				Diclofenac	Ibu
All Patients					
	n=3987	n=1996	n=1985		
No. of CSUGIEs/GDUs					
Uncensored	43	26	36		
Censored	3	1	2		
Total	46	27	38		
Week 52 crude rate†	1.05%	1.30%	1.76%	0.296	0.017	0.040
No. per 100 pt-yrs†	1.85	2.41	3.21		
Patients not Taking Aspirin					
	n=3105	n=1551	n=1573		
No. of CSUGIEs/GDUs					
Uncensored	21	10	28		
Censored	1	0	1		
Total	22	10	29		
Week 52 crude rate†	0.68%	0.64%	1.72%	0.992	<0.001	0.020
No. per 100 pt-yrs†	1.16	1.19	3.20		

Derived from Tables T20.1 through T21.3.
† Censoring rule applied.

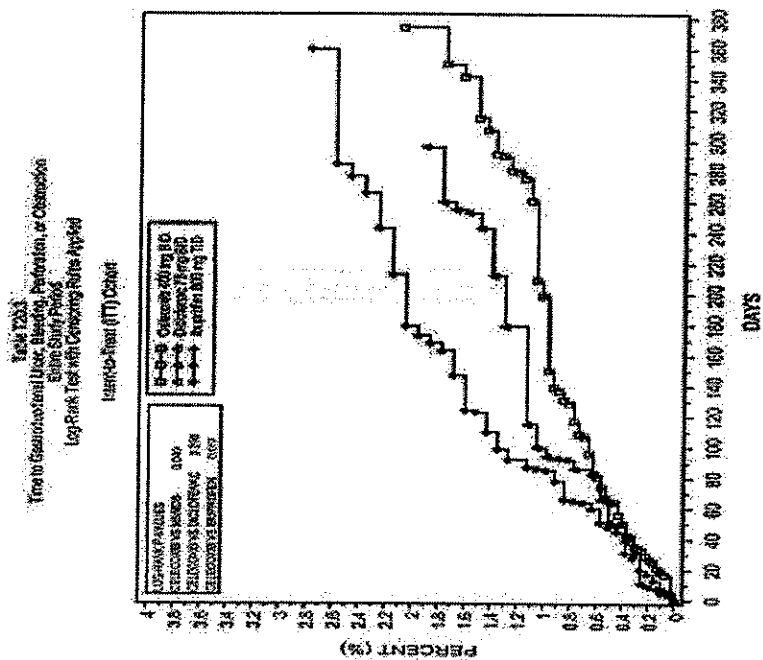**Table 8.j.** **Distributions of CSUGIEs/GDUs by Category: Traditional Definitions - Entire Study Period**

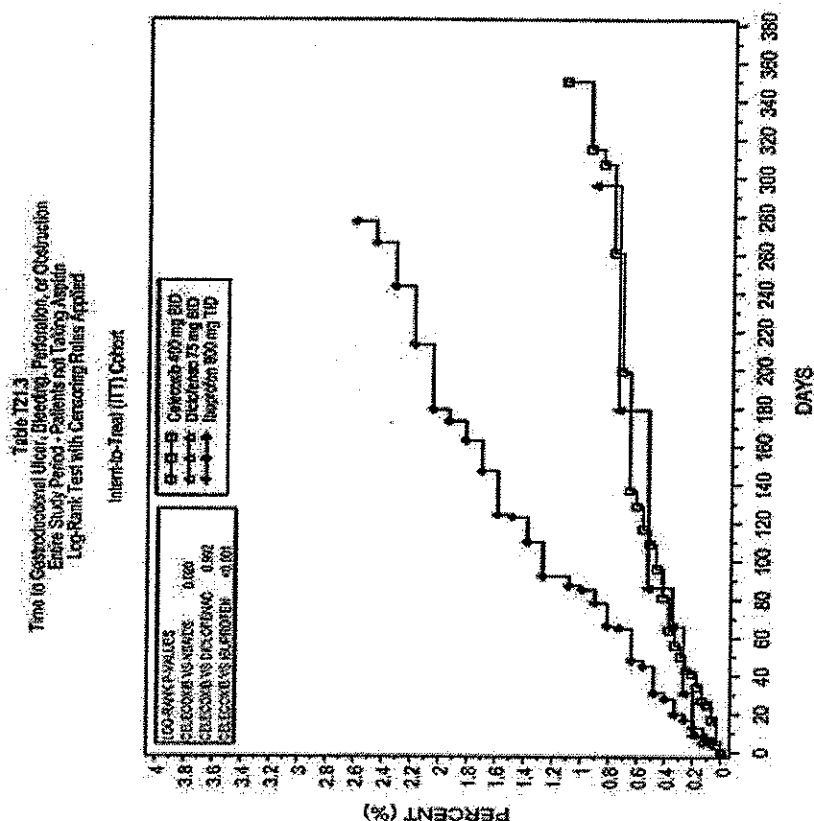| Event Category	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
UGI Bleeding (Category 1)			
1A: Hematemesis with ulcer/large erosion	1	--	--
1B: Ulcer/large erosion with evidence of bleeding	8	4	7
1C: Melena with ulcer/large erosion	5 *	4	3 *
1D-1: Hemoccult-positive stool with ulcer/large erosion and hematocrit/hemoglobin drop	3 †	2	3
1D-2: Hemoccult-positive stool with ulcer/large erosion and orthostasis	--	--	--
1D-3: Hemoccult-positive stool with ulcer/large erosion and transfusion	--	--	
1D-4: Hemoccult-positive stool with ulcer/large erosion and blood in stomach	--	--	--
UGI Perforation (Category 2)	1	1 †	--
Gastric Outlet Obstruction (Category 3)	2	--	--
Symptomatic Ulcers			
Gastroduodenal‡	26	16	25
Gastric	18	13	22
Duodenal	10	5	3
Total	46	27	38
Total Uncensored	43	26	36

Derived from Tables T22, T23.1 through T23.3 and Appendix 2.6.1. Entries are numbers of patients. See Section 6. 4. 3. 1. for full definitions.
* Two of these events censored from primary analysis. † One of these events censored.
‡ Any patient with both gastric and duodenal ulcers is counted once in the "Gastroduodenal" row.

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Table T21.3
Time to Gastroduodenal Ulcer, Bleeding, Perforation, or Obstruction
Entire Study Period - Patients Not Taking Aspirin
Log-Rank Test With Censoring Rules Applied

Intent-to-Treat (ITT) Cohort

CSUGIEs in aspirin users:

Although the primary hypothesis of this study and the biologic rationale for the use of COX-2 selective agents is to avoid the GI toxicity of traditional NSAIDs, there is a lack of scientific data to guide the use of cardioprotective doses of aspirin in patients requiring NSAIDs. One may expect additive toxicity from combined use of aspirin and NSAIDs. Given the reversible platelet inhibition associated with less selective COX inhibitors, some physicians may recommend only an NSAID in subjects who require such therapy in addition to being candidates for aspirin prophylaxis. The inclusion of aspirin users in this study has generated one of the best-controlled databases with which to address this issue.

Appendix 2.5.8 indicates that the use of aspirin increases the event rate in the C group to the range of diclofenac plus aspirin. Thus, there would be no GI safety rationale to the use of low dose aspirin plus C instead of diclofenac plus an aspirin. The results in the

ibuprofen group are somewhat surprising. The event rate is substantially lower with concomitant use of ibuprofen and aspirin use compared with ibuprofen alone. This is counter intuitive. One may suggest that the small numbers of events over time yield statistically meaningless results (see appendix 2.5.11).

However, the results of CSUGIEs/GDU (PUBs) stratified by aspirin use also reveals a loss of any benefit with the concomitant use of low dose aspirin. The same pattern of greater risk in the C and diclofenac groups compared to the ibuprofen group is seen in this endpoint as well as the CSUGIE endpoint. There appears to be a higher risk of concomitant ibuprofen and aspirin use than C and aspirin use (see appendix 2.5.12) Furthermore, a secondary endpoint, rates of reported potential CSUGIEs, suggested that clinical suggestive UGI presentations were similar in all groups with concomitant aspirin use. Thus it appears that tolerability as well as clinically serious UGI events is not better in patients taking C compared to both traditional NSAIDs in aspirin users. The current label for C, based on the endoscopic studies in the original NDA database, suggests that aspirin use in conjunction with C may still be "safer" than traditional NSAIDs. This statement should be revisited in light of this new more robust data.

Appendix 2.5.8
Clinically Significant UGI Event Rates by Time Interval - Traditional Definition
Entire Study Period - Patients Taking Aspirin
Crude and Kaplan-Meier Cumulative Event Rates

Intent-to-Treat (ITT) Cohort

Dosing Interval		Celecoxib 400 mg BID (N = 882)		Diclofenac 75 mg AID (N = 445)		Ibuprofen 800 mg TID (N = 412)	
		Censoring Rule Applied	Censoring Rule Not Applied	Censoring Rule Applied	Censoring Rule Not Applied	Censoring Rule Applied	Censoring Rule Not Applied
Crude Rates							
WEEK 1	(1 - 7)	0.00%	0.00%	0.33%	0.32%	0.00%	0.24%
WEEK 4	(8 - 28)	0.11%	0.11%	0.45%	0.45%	0.00%	0.24%
WEEK 13	(29 - 91)	0.34%	0.45%	0.90%	0.90%	0.00%	0.24%
WEEK 26	(92 - 182)	0.68%	0.79%	1.12%	1.12%	0.24%	0.49%
WEEK 39	(183 - 273)	0.79%	1.02%	1.35%	1.35%	0.24%	0.49%
WEEK 52	(274 - 364)	1.02%	1.25%	1.35%	1.57%	0.24%	0.49%
Kaplan-Meier Rates							
WEEK 2	(1 - 7)	0.69%	0.05%	0.23%	0.23%	0.02%	0.26%
WEEK 4	(8 - 28)	0.16%	0.16%	0.50%	0.50%	0.07%	0.31%
WEEK 13	(29 - 91)	0.50%	0.61%	1.10%	1.30%	0.22%	0.46%
WEEK 26	(92 - 182)	1.03%	1.16%	1.60%	1.60%	0.41%	0.65%
WEEK 39	(183 - 273)	1.33%	2.46%	1.80%	2.22%	-----	-----
WEEK 52	(274 - 364)	1.60%	1.93%	-----	2.31%	-----	-----

Note: Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval.
Uncensored events were defined as those meeting either of the following two conditions: 1. Occurred after 48 hours past midnight of the first dosing day and before 48 hours following midnight of the last dosing day. 2. Occurred after 48 hours past midnight of the last dosing day and before 2 weeks following midnight of the last dosing day and were determined to be causally related to study drug by the GI events committee. Events were censored if they failed to meet either of these two conditions.

Appendix 2.5.12
Gastroduodenal Ulcer, Bleeding, Perforation, or Obstruction Rates by Time Interval
Entire Study Period - Patients Taking Aspirin
Crude and Kaplan-Meier Cumulative Event Rates

Intent-to-Treat (ITT) Cohort

Dosing Interval		Celecoxib 400 mg BID (N = 882)		Diclofenac 75 mg BID (N = 446)		Ibuprofen 800 mg TID (N = 412)	
		Censoring Rule Applied	Censoring Rule Not Applied	Censoring Rule Applied	Censoring Rule Not Applied	Censoring Rule Applied	Censoring Rule Not Applied
Crude Rates							
WEEK 1	(1 - 7)	0.00%	0.00%	0.22%	0.22%	0.90%	0.24%
WEEK 4	(8 - 28)	0.34%	0.34%	0.45%	0.45%	0.90%	0.24%
WEEK 13	(29 - 91)	1.11%	1.25%	1.35%	1.35%	0.97%	1.21%
WEEK 26	(92 - 182)	1.85%	1.70%	2.47%	2.47%	1.46%	1.70%
WEEK 39	(183 - 273)	1.70%	1.93%	3.60%	3.60%	1.46%	1.70%
WEEK 52	(274 - 364)	2.38%	2.61%	3.60%	3.82%	1.95%	2.18%
Kaplan-Meier Rates							
WEEK 1	(1 - 7)	0.05%	0.05%	0.23%	0.23%	0.04%	0.26%
WEEK 4	(8 - 28)	0.47%	0.47%	0.62%	0.62%	0.17%	0.49%
WEEK 13	(29 - 91)	1.37%	1.41%	1.87%	1.87%	1.40%	1.64%
WEEK 26	(92 - 182)	2.16%	2.24%	3.48%	3.48%	2.08%	2.33%
WEEK 39	(183 - 273)	2.41%	2.75%	5.21%	5.60%	2.46%	2.72%
WEEK 52	(274 - 364)	3.94%	5.26%	.....	5.80%	3.33%	3.56%

Note: Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval.
Uncensored events were defined as those meeting either of the following two conditions: 1. Occurred after 48 hours past
midnight of the first dosing day and before 48 hours following midnight of the last dosing day. 2. Occurred after 48 hours
past midnight of the last dosing day and before 2 weeks following midnight of the last dosing day and were determined to be
causally related to study drug by the GI events committee. Events were censored if they failed to meet either of these two
conditions.

Appendix 2.5.17
Rates of Reported Potential CSUGIEs by Time Interval
First Six Months - Patients Taking Aspirin
Crude and Kaplan-Meier Cumulative Event Rates

Intent-to-Treat (ITT) Cohort

Dosing Interval	Celecoxib 400 mg BID (N = 833) Event Rate	Diclofenac 75 mg BID (N = 429) Event Rate	Ibuprofen 800 mg TID (N = 383) Event Rate
Crude Rates			
WEEK 1 (1 - 7)	3.09%	3.50%	2.87%
WEEK 4 (8 - 28)	6.69%	6.76%	8.36%
WEEK 13 (29 - 91)	13.23%	13.52%	15.93%
WEEK 26 (92 - 182)	16.45%	18.18%	18.54%
Kaplan-Meier Rates			
WEEK 1 (1 - 7)	3.04%	3.55%	3.43%
WEEK 4 (8 - 28)	6.83%	7.53%	8.66%
WEEK 13 (29 - 91)	14.81%	15.63%	17.94%
WEEK 26 (92 - 182)	19.25%	21.71%	21.99%

Note: Kaplan-Meier rates are based on the highest Kaplan-Meier estimates within that time interval.

Alternate definition results

The definition of the "alternate definition" may be found in Appendix I. This definition required a more serious bleeding event than the traditional definition. Given the lack of effect of C on platelet aggregation, one may expect a stronger nominal trend in favor of C in such an analysis

*The trends seen in sponsor's table 8.v. and 8.u. are not supportive of the hypothesis that C is associated with a lower rate of **bleeding** CSUGIEs than either ibuprofen or diclofenac.*

Table 8.v   Summary of CSUGIE Incidence: Alternate Definitions - Entire Study Period

	Celecoxib 400 mg BID (n=3987)	Diclofenac 75 mg BID (n=1996)	Ibuprofen 800 mg TID (n=1985)
No. of CSUGIEs			
Uncensored	17	5	9
Censored	2	1	1
Total	19	6	10
Week 52 crude rate†	0.43%	0.25%	0.45%

Derived from Tables T30.1 and T30.2.
† Censoring rule applied.